National Vulvodynia Association

NVA News

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FDA Approves First Non-Hormonal Treatment for Menopause-Associated Dyspareunia

Questions and Answers with Gloria Bachmann, MD, MMS

In addition to serving as the associate dean for women's health, Dr. Bachmann is a professor of obstetrics and gynecology and medicine, and interim chair of the obstetrics, gynecology and reproductive medicine department, at the University of Medicine and Dentistry of New Jersey – Robert Wood Johnson Medical School. Her clinical and research interests focus on women's gynecological and reproductive disorders, especially those experienced more so by aging women.

NVA: What is vulvar and vaginal atrophy and how common is it?

Dr. Bachmann: Vulvar and vaginal atrophy (VVA) is a chronic postmenopausal health condition that occurs when the tissue is deprived of estrogen. Less estrogen makes vulvovaginal tissue thin, dry and fragile, i.e., atrophic. The condition is common, under-reported, and unlike other symptoms of menopause that lessen or cease with time (e.g., hot flushes), painful intercourse, vaginal dryness, itching and irritation caused by VVA usually persist and can even worsen without treatment. Among postmenopausal women who have never used menopausal hormone therapy, Santoro (2009) found the incidence of VVA symptoms, including painful sex, to be as high as

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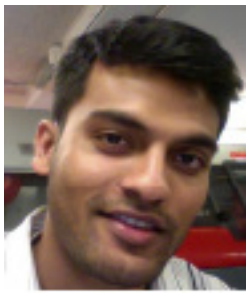
Vulvodynia Subgroups Show Differences in Brain Activity

By Johnson Hampson, MSBME, Richard Harris, PhD, and Barbara Reed, MD, MSPH

Mr. Hampson (pictured on right) holds a master's degree of science in biomedical engineering and is on the research staff at the Chronic Pain and Fatigue Research Center in the department of anesthesiology at the University of Michigan in Ann Arbor. Dr. Harris (pictured on p. 14) is an assistant professor in the same department, with a professional interest in chronic pain and neuroimaging. Dr. Reed (pictured on p. 14) is a professor of family medicine at the same institution, and has received several research grants from the National Institutes of Health to study various aspects of vulvodynia, including underlying mechanisms of pathophysiology.



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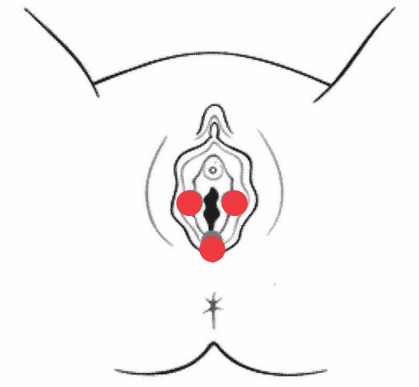
Definitions and Types of Vulvodynia

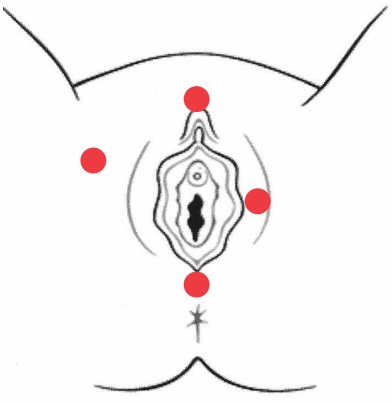
Many different terms have been used to describe vulvodynia. As a result, confusion among patients and medical professionals is common. To encourage consensus and clarify terms used in this newsletter, we have provided a brief summary of the most current definitions and classification. For more detailed information, please see slides 3-5, 15 and 16 at http://LearnProvider.nva.org.

Vulvodynia is *chronic (more than three to six months) vulvar pain without an identifiable cause*. The location, constancy and severity of the pain vary among women. The two main subtypes of vulvodynia, which may co-exist, are:



Provoked Vestibulodynia (PVD)
(Previously: Vulvar Vestibulitis Syndrome)

Women with PVD only have pain in the vestibule (around the vaginal opening) that occurs during/after touch or pressure, e.g., with intercourse, tampon insertion, prolonged sitting. PVD is further classified as *primary (pain since the first attempt at penetration*) or *secondary (pain that starts after a period of pain-free penetration*).



Generalized Vulvodynia (GVD)
(Previously: Dysesthetic or Essential Vulvodynia)

Women with GVD have spontaneous pain in multiple areas of the vulva. It is relatively constant, but there can be some periods of symptom relief. Activities that apply touch or pressure to the vulva, such as prolonged sitting or simply wearing pants, typically exacerbate symptoms.

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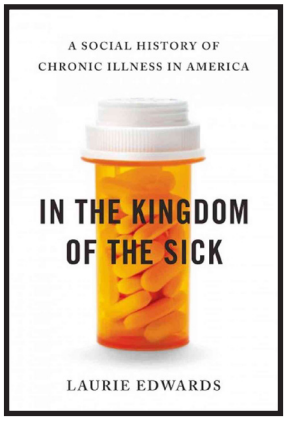
The National Vulvodynia Association is a nonprofit organization that strives to improve women's lives through education, support, advocacy and research funding.

The NVA is not a medical authority and strongly recommends that you consult your own health care provider regarding any course of treatment or medication.

In the Kingdom of the Sick: A Social History of Chronic Illness in America



By Laurie Edwards

Ms. Edwards teaches health writing at Northeastern University, and her own work has appeared in the New York Times, Boston Globe Magazine, Glamour *and many online and print outlets. Her first book,* Life Disrupted: Getting Real About Chronic Illness in Your Twenties and Thirties*, was named one of 2008's best consumer health books. She's a lifelong sufferer of chronic illness, and first began writing about the topic in young adults in her blog,* A Chronic Dose*. Her newest book,* In the Kingdom of the Sick*, published in April 2013 by Walker & Company, explores the issues of importance to people who are sick or well, from patient rights and the role of social media in medical advocacy to the origins of our attitudes about illness and much more.*

Excerpt from Chapter 6 - A Slight Hysterical Tendency: Revisiting "The Girl Who Cried Pain"

"People often underestimate how much pain I'm in because I don't spend a lot of time complaining about it," Melissa McLaughlin says. "Doctors seem to think I'm exaggerating my number scale of pain because if I were in that much pain, I wouldn't be functioning, they think. But here's the thing: I don't have a choice… my pain is my pain, and if there's going to be anything else in my life, I have to work through and past it, regardless of how high it is."

It's an untenable situation: patients are considered lazy or indulgent if they remain housebound, but should they manage some activity or productivity, then their pain can't be as severe and exhausting as they claim. Here again we see the contradiction so common in the social history of disease: the absence of outward physical manifestations of illness somehow negates the actual experience of having it. Rather than over-reporting pain, as critics suggest chronic pain patients of all varieties do, McLaughlin and others cop to regularly under-reporting it, aligning them more closely with classic "male" stereotypes.

To McLaughlin, labeling her pain as the normal aches that healthy people learn to ignore, as skeptics have characterized fibromyalgia pain, is woefully inaccurate — and unfair. Yet it is something she deals with from friends and family, and especially from health care providers. In the years since she went from a normal, healthy teenager to an adult in chronic pain, she honestly can't count the number of times her pain has been dismissed, overlooked, or underestimated by a doctor: "Of course you're exhausted, you're working too hard" or "You can't still be in pain, that should've gotten better by now" or "I don't understand how your pain can be worse now than it was the last time I saw you," are common refrains. When it comes to the severity of her pain, the standard scale is a poor substitute.

"Telling them I'm an eight out of 10 on the pain scale — on a fairly regular basis — doesn't seem to mean as much to them as it does to me," McLaughlin says. They're looking for static indices of dis-

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Chronic Illness

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ease, while she is looking for a way to lead a normal life, to leave the house, hold down a job, someday have a family of her own, to reclaim the social ties and roles her severe, unrelenting pain has taken away from her.

Pain specialists like Dr. [Sarah] Whitman urge an integrated model of treatment that doesn't rely solely on medication and procedures but also focuses on behavioral changes, education and advocacy. If we looked at chronic pain the same way we approach treating a disease like diabetes, whose regimen includes diet, exercise, and lifestyle changes in addition to medication, then perhaps we could begin to distance ourselves from the notion that if we could just "cure" chronic pain, we would be all set.

How much of this gap in diagnosis and treatment is also due to the assumptions physicians and patients bring to their relationship? Here is where the social cues and mores that manifest in the profoundly human interaction between doctor and patient exert their influence. Barbara Kivowitz is a well-educated middle-aged woman, a former therapist who is now a consultant. She is an informed patient and not afraid to speak her mind. Yet she noticed two significant trends in her encounters with physicians. First, when she described her pain, it was often in emotional terms – how miserable she was, how frustrated, how her severe pain impacted her life.

"I wouldn't hold back. I would assume that my experience of my pain and my feelings about it and intuitions about it were data. For a lot of doctors, that wasn't data," she says. In those moments, she detected impatience in her physicians' demeanor, a resistance to her display of emotions. Second, she noticed a dynamic when her partner, a male, joined her for appointments. He asked questions she would never think to ask, and approached things from an entirely different perspective.

"I do wonder if having the male in the room does automatically up the credibility curve a little bit," she says. She started talking about her symptoms differently, as if she were a scientist. First she had handwritten score charts of pain spikes and dips and would show the chart. She became deliberate and conscious about when she would release any emotion, and the release was controlled and put within the context of analytic data, establishing more credibility in her reporting.

Kivowitz's distinction between feelings and intuitions as data versus concrete numbers is particularly compelling in light of research that shows that men and women describe complex pain very differently. A 2008 study found that while women described their symptoms in vague, abstract terms, men used simple, concrete terms. Rather than illustrating how the pain influenced certain activities or emotions, men reported what hurt and where. As such, it was easier for doctors to hazard a diagnosis and then move on to the appropriate course of treatment for their male patients. This research also fits in with earlier studies on gender roles and communication analyzed in "The Girl Who Cried Pain," which found that women were more likely to describe their pain within the context of their relationships and social networks [Hoffman et al. Am J L & Med. 2001].

Combined with previous data, these findings are actually promising. They provide a theoretical foundation for the fact that some of the reason women feel dismissed or undervalued when they seek treatment for pain isn't because they are inherently too emotional or too prone to complaining (as we know), but that they are "speaking another language." This is not to say that women are to blame for the lag in diagnosis and treatment. Rather, it points to some

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Chronic Illness

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of the possible reasons why this pattern continues, and why physicians and patients alike should consider their modes of communication.

These findings also point to an important difference in the way both parties approach this pivotal interaction: physicians are interested in analyzing pain, whereas patients, many of whom have lived with pain for years, are less focused on the analysis of pain itself and more concerned with alternatives to their current pain management. When you consider the distinction between disease (that which can be quantified by tests and results) and illness (the subjective experience of living with a condition), this makes sense.

Toward an Answer: Pain in the 21st Century

"I'm an optimist by nature, but I believe there's evidence to support a hopeful outlook. The gains which will come soonest - which actually are occurring as we speak - are advances in the understanding and treatment of pain, regardless of gender," says Dr. Whitman. "One which will be crucial is a better biological understanding of pain- viewing it as a medical disease, rather than a psychological weakness. Because women are disproportionately affected by pain, this will benefit them the most."

In a critical review of pain research published in the *Journal of Pain* in 2009 [Fillingim et al., "Sex, Gender, and Pain"], researchers found that "abundant evidence from recent epidemiologic studies clearly demonstrates that women are at substantially greater risk for many clinical pain conditions, and there is some suggestion that postoperative and procedural pain may be more severe among women than men... current human findings regarding sex differences in experimental pain indicate greater pain sensitivity among females compared with males for most pain modalities..."

Based on her experiences working with patients in pain of both genders, Dr. Whitman offers five specific steps she thinks can help society move forward when it comes to treating women in pain: improved education about pain in general; educating ourselves about our own medical conditions and treatment options; seeking a second or alternative opinion and questioning doctors; supporting organizations that seek to educate the public about pain or that support research in pain diseases; and advocating for increased research spending by the National Institutes of Health. She makes this last suggestion with good reason: while chronic pain is as prevalent as cancer, cardiovascular disease, and diabetes combined, the NIH spends 96 percent less on research on chronic pain than on these conditions.

We've seen some progress. In 2011, the United States Senate called for an expanded and better-coordinated research effort for several pain conditions, including chronic fatigue syndrome, fibromyalgia, [vulvodynia] and endometriosis, and under the auspices of the Affordable Care Act, the NIH asked the Institute of Medicine to address the public health impact of chronic pain and come up with specific recommendations to improve how

> *"Illness is the night side of life, a more onerous citizenship. Everyone who is born holds dual citizenship, in the kingdom of the well and in the kingdom of the sick. Although we all prefer to use the good passport, sooner or later each of us is obliged, at least for a spell, to identify ourselves as citizens of that other place."*
>
> *Susan Sontag*
> *Illness as Metaphor, 1978*

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In Her Own Words

By Erin Kristoff

The details of my initial struggle with vulvodynia are no more or less important than many others. Though the various treatments and new pelvic pain diagnoses that followed seem outrageous and perplexing to my loved ones and friends, I know from speaking with other members of this special community that it is not that different a story from many of you.

Who would guess that the most interesting aspect of my story with vulvodynia is where I found myself now – in the middle of my journey – somewhere between sick and healed?

A few months ago, my nearly two-year battle with pain finally landed me in the office of a competent gynecologist who was a genuine specialist in this medical area. For three hours we talked about my different levels and types of pain. Did it feel sharp or sore, tingling or numbing? By the end of the appointment I had a cotton-swab test, cultures, blood drawn and two different pelvic exams. I was physically spent, but the mental exhaustion would ultimately be what cut me off at the knees.

While I felt so blessed to have at last found a competent physician, he found that I was actually in worse shape than I thought. In addition to vulvodynia, I now had lichen sclerosus and ulcerations, as well as pelvic floor muscle dysfunction and possibly pudendal nerve issues. With referrals for physical therapists and physiatrists in hand, I walked out of his office in a daze – caught between conflicting emotions. I felt great relief that I was in the right hands, but I was also angry that my previous doctors hadn't noticed these seemingly obvious problems. On top of that, I felt hurt by how far it had progressed and what I had lost.

I didn't realize it for several days, but I was slipping into a deep depression. I no longer had the will to keep up with my life. I went through the motions at work, took my new medications with little hope of them working and made dinner for my boyfriend without the usual zest I have when cooking. I didn't try to spend time with my family or friends. I just didn't care.

When it finally sunk in that I was in emotional pain, I was lucky enough to be standing in front of the NVA newsletter with a small piece about another woman's story and depression. The article lifted me up just enough to want to help myself break out of the fog. I started a gratitude journal and every night before I went to bed, I found at least one thing that I was grateful for in that day. It could be as big as feeling huge pain relief, or as small as seeing my puppy's face when I got home from a hard painful day. Although this exercise helped me go to sleep with positivity in my heart, I still had an overwhelming sense of loss and isolation.

At the end of April I went to a retreat for women suffering from chronic pelvic pain. I learned a lot there, but the most important thing I came away with was the quality friendships I made – one in particular that changed my entire view on being sick. It felt amazing to meet others like me, especially young girls facing many of the same issues I face. One woman told me her story and I felt so inspired. She looked me in the eye and said, "You will get better. I swear to you, you will get better." Instantly, I believed her. She also told me a story about a dark time in her life when she stumbled on someone who pulled her out of the fog. Her friend had placed his hands on the far left and right of his desk and told her, "You are here. And you need to get here. And everything in between is getting you one step closer to healed."

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Reason for Hope

An Update from NVA's Executive Director

Dear NVA Friend,

Even the eternal optimist can experience periods of sadness, frustration, despair and isolation when dealing with the daily challenges imposed by vulvodynia. If you are anything like me, it's so important, especially during the most difficult times, to be reminded of all that's underway to improve our health and quality of life. There is a tremendous amount of behind-the-scenes work that goes on at the NVA, with more awareness, educational, clinical and scientific initiatives on vulvodynia, women's sexual health, and chronic pain in women than ever before. There *is* reason for you and I to have hope today – both for ourselves and the women and girls who will come after us.

As highlighted on page one, the FDA recently approved the first non-hormonal treatment for painful intercourse due to menopause-associated vulvovaginal atrophy. As part of the manufacturer's associated awareness effort, actress Virginia Madsen has stepped forward as the first celebrity spokesperson to address the long-overlooked and life-altering issue of painful intercourse. (For more information, please see www.findingthewords.com.) Although vulvodynia encompasses so much more than painful sex, impacting all facets of women's lives, the FDA's approval of this treatment and subsequent awareness effort are significant in several ways. First, the pharmaceutical industry has not only come to understand the imperative need for novel, effective treatments for vulvovaginal pain disorders, but they've begun to commit to this area by investing significant funds – to identify potential treatment targets, conduct the necessary safety and efficacy research and bring promising solutions to market. Additionally, this particular treatment and effort were developed specifically for postmenopausal women – a group that has historically been excluded from many clinical and scientific efforts. Finally, having a celebrity come forward to openly discuss this long-silent issue is pivotal to furthering a national conversation on these disorders and their grave impact on women's health and quality of life.

Thanks to the commitment of a generous NVA donor, we've also educated a record number of clinicians in the fields of gynecology, family medicine, women's health, pediatrics and others, about vulvodynia through our new online Medscape course. By including the most recent high-caliber scientific findings in this program, which offers continuing medical education credit to all medical professionals, in a little over two months, we've provided more than 25,000 clinicians with the very latest and best information on the medical management of vulvodynia. We were extremely pleased to learn that the majority of those completing the course post-test indicated that they were committed to altering how they practice medicine by using course information to modify their screening, diagnostic and treatment practices, and 90 percent said they'd recommend the program to colleagues! (To view the program, visit: http://learnprovider.nva.org.)

The NVA was pleased to work with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development to plan and convene a workshop in May, *Facilitating Scientific Advancement of Vulvodynia through the Development of Research Diagnostic Criteria (RDC)*. The two-day meeting

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Menopause

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60 percent. Further, both sexually active women and those who weren't engaging in sexual activity were equally likely to be affected by these symptoms. Despite VVA's negative impact on physical and sexual function, psychosocial well-being and partner relationships, it frequently goes untreated.

NVA: What treatments are available to manage the symptoms of VVA?
Dr. Bachmann: For women experiencing this problem for the first time, over-the-counter lubricants and moisturizers are recommended. Finding the best one for you is usually arrived at by trial and error. For menopausal women who don't achieve a desired effect, low-dose, vaginally administered estrogen-based agents are usually effective. Due to safety concerns, many women stopped using oral estrogen plus progestin hormone therapy after the findings of the Women's Health Initiative (WHI) study were published, even though the WHI only studied oral (and not vaginal) hormonal therapies. Currently, *oral* estrogen or oral estrogen plus progestin therapy is not recommended for women who desire treatment for their VVA symptoms; rather, low-dose *vaginal* estrogen products, usually prescribed without a progestin, are recommended.

NVA: Should certain women avoid vaginal use of estrogen?
Dr. Bachmann: Vaginal estrogen is not a good option for women who have had an estrogen sensitive cancer or who may be at high risk for a blood clot or stroke. Additionally, this treatment isn't viable for women who either don't want or are unable to use or administer a vaginal product because of vulvodynia or another condition.

NVA: Are other treatments being studied?
Dr. Bachmann: Yes, selective estrogen receptor modulators (SERMs) are currently of great interest. SERMs are a class of compounds that act on the estrogen receptor. The distinguishing characteristic, however, is that different SERMs act disparately in selective tissues (e.g., breast, vaginal, endometrial, bone), and can therefore be used to selectively inhibit or stimulate estrogen-like action in the specific tissue of interest without affecting other areas. Tissue selectivity is a key characteristic of SERMs that affects their effectiveness and safety, and ultimately their viability as a treatment. An ideal SERM for treating VVA should act directly on vaginal tissue, but not affect breast and endometrial tissues. A new treatment option, ospemifene (Osphena), is a SERM that was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of menopausal women who have dyspareunia, i.e., painful sex, due to VVA. I recently participated in a large clinical network that studied the effectiveness of this novel treatment in menopausal women.

NVA: Does ospemifene have some estrogen-like effects?
Dr. Bachmann: Yes, it acts like estrogen on vulvovaginal tissue to make it thicker and less fragile, which results in less pain with sexual activity.

NVA: What studies on ospemifene's safety and effectiveness did the FDA review?
Dr. Bachmann: In all, the FDA reviewed three clinical studies of nearly 2,000 postmenopausal women to determine ospemifene's safety and effectiveness in treating symptoms associated with VVA, including painful intercourse. As a member of the ospemifene study group, I was involved in these studies, the latest of which was recently published in *Menopause* and summarizes data on the largest cohort of 600 postmenopausal women

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(aged 40 to 80) studied. A randomized, double-blind, parallel-group design was used to compare the effectiveness, safety and tolerability of ospemifene 60mg/day versus placebo in treating moderate to severe dyspareunia due to VVA.

NVA: What did the study entail?
Dr. Bachmann: Women were screened by assessing their most bothersome symptom on a four-point scale (0, none; 1, mild; 2, moderate; 3, severe). Those reporting moderate or severe vulvovaginal pain with sexual activity as their most bothersome symptom continued to the next phase of the trial. Women were diagnosed as having VVA if they had five percent or less superficial cells in the maturation index of the vaginal smear and a vaginal pH higher than 5. To enroll, women had to have either had a hysterectomy or an intact uterus with a double-layer endometrial thickness less than 4mm and no evidence of hyperplasia, cancer or other pathology, as determined by an endometrial biopsy.

In the treatment phase, at 110 medical sites across the country, half of trial participants received 60 mg ospemifene, and the other half placebo medication, once daily for 12 weeks. Additionally, all of the women in the trial were given a non-hormonal vaginal lubricant to use as needed for on-demand comfort during sexual activity, and were asked to report lubricant use in a daily diary. Participants were seen on weeks 4 and 12 for completion of the VVA symptom questionnaire, assessment of vaginal pH, vaginal smear and visual examination of the vagina and vulva. Additionally, during the 12-week visit, women underwent a transvaginal ultrasound and endometrial tissue biopsy.

NVA: What were the study findings?
Dr. Bachmann: Compared to women taking the placebo medication, after 12 weeks, women using ospemifene demonstrated statistically significant efficacy for each of the four primary endpoints. The percentage of women reporting no/mild dyspareunia was greater in the ospemifene group (63 percent) than in the placebo group (47 percent). The severity of pain associated with sexual activity improved by two to three levels in 53 percent of women in the treatment group compared with 39 percent in the placebo group. (A three-level improvement was defined as a change from "severe" to "none," and a two-level improvement was either a change from "severe" to "mild" or from "moderate" to "none.") Women used less of the lubricant in the ospemifene group compared with the placebo group, despite no decrease in the frequency of sexual activity in either of the two groups. Additionally, the mean reduction in vaginal pH in the treatment group (-0.94) was greater than that in the placebo group (-0.07); the percentage of parabasal cells decreased by 40 percent in the ospemifene group, compared to no reduction in the placebo group; and the percentage of superficial cells increased by 12 percent in the ospemifene group, compared to two percent in the placebo group.

NVA: What side effects did women experience?
Dr. Bachmann: The most common side effect experienced was hot flushes, reported by nearly seven percent of women in the ospemifene group and four percent in the placebo group. The other adverse events, which occurred in less than six percent of the study participants, were urinary tract infection, vaginal candidiasis, vaginal discharge, vulvovaginal mycotic infections, nasopharyngitis (i.e., nasal inflammation) and headache.

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NVA: What safety concerns has the FDA voiced?

Dr. Bachmann: In general, as with other treatments, the FDA advises women to use, and clinicians to prescribe, ospemifene for the shortest duration consistent with treatment goals and with consideration of the contraindications for use in each woman. The treatment has been approved with a boxed warning alerting women and clinicians that the drug has been shown to stimulate the endometrium and cause it to thicken, which can cause bleeding (similar to what premenopausal women experience with monthly menstruation). From study results, it was noted that ospemifene caused a slight increase in endometrial thickness; however, after 12 weeks, no cases of endometrial hyperplasia, polyps or cancer were observed in endometrial biopsy samples from either study group. Another 12-week initial efficacy and safety study with an additional 40 weeks of long-term safety data demonstrated no clinically meaningful endometrial changes with long-term daily use in 180 women with VVA; further, a 52-week study found minimal estrogenic effects on the endometrium (Simon 2012, Goldstein 2011).

With the safety of women in mind, however, the FDA has advised women who experience unusual bleeding to consult their clinicians as this can be a sign of endometrial cancer or a condition that can lead to it. The boxed warning also states a low risk of stroke and deep vein thrombosis (i.e., blood clots), compared to the risk seen in estrogen-alone therapy.

NVA: What is the historical significance of the FDA approving ospemifene?

Dr. Bachmann: As stated prior, a significant percentage of postmenopausal women suffer from VVA and resultant dyspareunia, which affects many aspects of their physical, emotional and relational well-being. It's very encouraging to see a new therapeutic option approved by the FDA to manage the distressing issues that stem from painful intercourse caused by postmenopausal VVA. Women are living longer and many continue to be sexually active past menopause. This new treatment has the potential to help a significant number of women to achieve improved quality of life and relationship satisfaction.

[*Editor's Note: The results of ospemifene studies are more fully reported in: Portman DJ, Bachmann GA, Simon JA, and the Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy.* Menopause *2013;20(6):623-30.*]

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Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med.* 2009;6:2133-42.

Simon JA, Lin VH, Radovich C, Bachmann GA; the Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. *Menopause*. 2012 Nov 8. ■

Reason for Hope

(from page 7)

brought together federal scientific program officers and expert clinicians and researchers with the aim of developing: (i) vulvodynia RDC for inclusion in future vulvodynia studies and (ii) common data elements to be collected and outcome measures (particularly those that can differentiate subgroups) for investigators to use in all vulvodynia studies to facilitate the comparison and interpretation of study populations and findings as the field advances. This intitative is essential to advancing scientific efforts in a strategic, coordinated and time-efficient manner, and we look forward to updating you as it progresses.

Thanks to our donors' generosity, the NVA's Executive Board was recently able to approve funding for four new research projects, as well as the development of another new vulvar pain clinic. Based on a recent breakthrough in back pain research, Melissa Farmer, PhD, of Northwestern University, will conduct the first study to investigate central and peripheral nervous system changes occurring during the time when acute (less than three months) vulvar pain transitions to a chronic disorder, with the ultimate goal of identifying therapeutic interventions to prevent the development of vulvodynia. Based on recent evidence from the cancer pain field implicating the involvement of specialized enzymes called serine proteases in the development of abnormal pain processing, Steven Witkin, PhD, of Cornell University, will initiate the first exploration of these enzymes and inhibiting compounds in vaginal secretions of women with provoked vestibulodynia (PVD, aka vulvar vestibulitis) before and after treatment. This study will provide important information on a novel, biologically plausible and previously unexplored mechanism that may be involved in the development and perpetuation of PVD, and that can be targeted in treatment efforts.

Lee Hullender Rubin, DAOM, LAc, of the Oregon College of Oriental Medicine, will conduct a 12-week trial to determine the effectiveness of an acupuncture regimen versus topical lidocaine treatment in reducing vulvar pain severity in women with PVD. Using a special mouse model, Gerard Ahern, PhD, of Georgetown University, will direct the first study to map nociceptive, i.e., pain-sensing, nerve pathways in the vulva and vaginal opening. He will also measure two key pain receptors that are found throughout the body, but have yet to be characterized in vulvovaginal tissue – TRPV1 and TRPA1 – at different points throughout the reproductive cycle and in a post-menopausal state. The results will reveal important information regarding nociceptive signaling pathways that is needed to expand our understanding of vulvodynia mechanisms. Erin Gross, MD, of the University of California, San Diego (UCSD), was recently named the 2013 *Dr. Stanley C. Marinoff Vulvodynia Career Development Award* recipient. With this grant, and matching funds from her university, she'll develop the first comprehensive vulvar pain specialty clinic at UCSD and educate medical residents about the diagnosis and treatment of the disorder. (See full summaries of these projects at: www.nva.org/research_fund.html, and www.nva.org/career_development_award.html.)

Pertaining more generally to chronic pain, new federal initiatives hold the promise of advancing much-needed scientific and clinical efforts for all pain sufferers, including women and girls with vulvodynia. These include the NIH Centers of Excellence in Pain Education (see http://painconsortium.nih.gov/CoEPEs.html); the FDA-University of Rochester public-private partnership, *Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks* (see www.acttion.org);

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Clinical Trial Recruiting Participants in Memphis (TN) and Rochester (NY)

A Multicenter Controlled Trial of Gabapentin-ER in Vulvodynia: Biological Correlates of Response

If you suffer from vulvodynia and are 18 or older, you may be eligible to participate in this study to determine the effectiveness of Gabapentin-ER in relieving symptoms associated with provoked vestibulodynia (PVD, aka vulvar vestibulitis syndrome). Gabapentin – an anti-seizure medication that is currently approved for the treatment of neuropathic pain – may also be effective in treating other types of chronic pain, such as PVD. All study participants will receive both the active and placebo medications over the course of the trial. Participation is voluntary, and involves seven visits over an 18-week period. You will be asked to keep a daily electronic diary to record your pain.

To learn more, please visit www.HopeForMyPain.org. For additional information on participating in Tennessee, contact Leslie Rawlinson by phone (901-448-1500) or email (lrawlins@uthsc.edu). For information on participating in New York, contact Linda Closs Leoni, RN, MS, by phone (585-275-3160) or email (linda_leoni@urmc.rochester.edu). The Principal Investigators of this study are Drs. Candace Brown and David Foster. ■

In Her Own Words

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Over the course of the weekend I kept replaying these words in my head and I started to understand. All the new diagnoses and treatments were just extra clues to the puzzle. I will keep piecing them together until I've solved the whole darn thing.

I was talking about some of my coping mechanisms when one of the younger girls came up to me and said, "You are such an inspiration!" I was floored! Me? Ms. Cries-A-Lot? That's when I realized that we're all just rungs on a ladder. No matter how low you think you are, someone else might be looking up and thinking they would rather be there.

So now I take it one day at a time and fill my day with as much positivity as I can. I no longer look at the road before me with fear of the seemingly endless obstacles I'll meet, but with a feeling of endless possibility and hope. ■

Chronic Illness

(from page 5)

we research, treat, and understand pain. Approaching this report from a public health perspective inherently validates pain as a widespread, serious health issue.

Sontag's description of that "night side of life," wherein the sick dwell and which the healthy avoid, is especially fitting when it comes to those suffering from chronic pain. Brain, body, heart, mind-severe and ongoing pain encompasses every aspect of a patient's being, fills in so many crevices of his or her life, until it threatens to absorb them entirely. Since the development, experience, and perception of pain are influenced by a variety of factors, we should expect no less comprehensive an approach toward researching and potentially treating it. Science holds the power to at least partially demystify pain, but only if viewed within the context of the societal norms that shape the individual patient's world. ■

Stay Informed of the Latest Discoveries and Connect with the Research Community on the Pain Research Forum

The Pain Research Forum (PRF) – the only interactive online community and resource for the pain research community – unites basic, clinical and translational investigators and encourages improved communication and information sharing. The ultimate goal is to improve the lives of those suffering from chronic pain by advancing progress through collaboration.

Open dialogue and rapid information exchange will speed the development and utilization of new treatments for chronic pain, however, the pain research community suffers from fragmentation across many scientific/clinical disciplines and departments that rely on disparate conferences and journals to stay informed, exchange information and collaborate. The PRF addresses this problem by providing the entire community with a single venue within which to stay informed of the latest discoveries and news, access resources and community information and contribute to emerging pain research trends. Importantly, it is editorially independent, and content is free of advertising, political, commercial, foundation, university or other influences. Conference reports, weekly news stories, commentaries, discussions, monthly webinars and Papers of the Week—a listing of the most important pain research findings appearing in the literature—make the PRF a vital source of the latest discoveries and debates in pain research. Other new content under development includes databases of pain genes and drug development.

With support from a three-year pilot grant from two charitable foundations, the Forum was developed and launched in June 2011 as a joint project of the Harvard NeuroDiscovery Center and the Mass-General Institute for Neurodegenerative Disease Informatics group. The PRF is guided by an international advisory board of leading pain researchers. Since its launch, reaction from the biomedical research community has been excellent. More than 1,000 researchers, clinicians and others from over 40 countries have joined the project. Members are predominantly basic and clinical researchers with MD, PhD or related degrees, graduate students or post-doctoral fellows, from the academic, commercial and regulatory communities. To learn more, please visit www.PainResearchForum.org. ■

Reason for Hope

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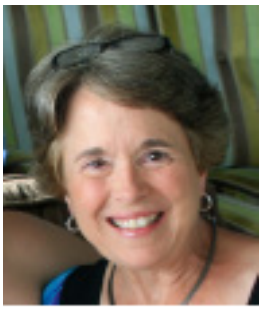
the FDA's Patient-Focused Drug Development initiative (see www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm349133.htm); and the Interagency Pain Research Coordinating Committee's new initiative to develop a national strategy for pain research, treatment, care and prevention (see http://iprcc.nih.gov/National_Pain_Strategy/NPS_Main.htm). The NVA is involved in many of these initiatives and is diligently working to ensure that national endeavors like these include a long-overdue focus on vulvodynia and related pain disorders. We look forward to sharing more with you as these projects advance.

Thank you for your continued generosity, which makes all of our work possible! Please consider contributing to our summer fundraising effort to support vulvodynia research securely online at www.nva.org/join_donate_renew.html.

With sincere gratitude,
Christin Veasley, *NVA Executive Director*

Brain Activity

(from page 1)



Millions of women suffer from vulvodynia (VVD), yet little is known about the disorder's causes and underlying mechanisms. Research conducted to date has shown that in addition to having lower pain thresholds in vulvar tissue, women are also more sensitive to experimental pain measures in other parts of their bodies, such as the thumb, arm and shin (Foster 2005, Giesecke 2004). This body-wide sensitivity suggests that the central nervous system (CNS, i.e., brain and spinal cord) may play a role in the disorder's underlying pathophysiology. One way to "see" how the CNS processes pain is through functional magnetic resonance imaging (fMRI). Numerous studies have shown that a number of brain regions are activated when a person experiences pain; these areas (pictured on p. 16) – often referred to as the "pain matrix" – include pronociceptive regions (i.e., regions that amplify pain perception), such as the insula (aIC and pIC), thalamus (THAL), posterior cingulate (PCC), mid-cingulate (MCC), somatosensory cortex (S1 and S2), and amygdala (AMY), as well as anti-nociceptive regions (i.e., regions that inhibit pain perception), such as the dorsolateral prefrontal cortex (DLPFC), anterior cingulate (ACC), peri-aqueductal gray (PAG), and rostral ventromedial medulla (RVM).

In the only prior fMRI study of women with vulvodynia, significant activation of the insular cortex, somatosensory cortex and premotor cortex were observed when experimental pressure pain was applied to painful vulvar tissue (Pukall 2005). In our study, the results of which were recently published in *The Journal of Pain*, we sought to investigate how the brains of women with VVD would respond when we applied experimental pressure pain not only to the vulva, but also to a body site distant to the vulva, i.e., the thumb. In addition to comparing VVD patients to healthy controls, we also compared them to women with fibromyalgia (FM) who had previously undergone the same fMRI protocol to determine whether the two disorders have similar altered CNS activity. Additionally, because research suggests that multiple underlying mechanisms may be responsible for triggering, causing and/or maintaining VVD symptoms, we also subdivided women into distinct groups to assess whether brain alterations differed by subtype assignment.

The final analyses included data on 61 women aged 18 to 60 years – 24 women with VVD, the same number of women with FM, and 13 controls. VVD participants were included if they had pain at the opening of the vagina for at least three months with no other vulvar disorder that would explain the pain. All women completed a detailed questionnaire that asked about their symptom history and pain characteristics. Vulvodynia patients and controls also underwent a thorough gynecological examination that included visual inspection, cotton-swab testing at 27 vulvar sites and a vaginal inspection, which included the assessment of vaginal secretions and a yeast culture to rule-out infection. Vulvodynia subgroups were then characterized as: primary (pain present since the first intercourse or tampon use) versus secondary (pain occurring after a period when intercourse or tampon use was not painful); provoked

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Brain Activity

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(pain occurring only with intercourse, tampon use or touch) versus unprovoked (pain that spontaneously occurs without touch or pressure); and localized (pain localized to the vaginal opening only) versus generalized (pain in multiple vulvar areas).

Prior to undergoing the fMRI, women with VVD and controls underwent a pressure pain test at both the thumb and vulva, and women with FM had thumb testing only. In brief, increasing pressure was administered to either the vulva or thumb until women indicated that the pressure elicited moderately severe pain (using the Gracely Box Scale), and then this pressure amount was recorded. Women's clinical pain experience was also assessed using the short form of the McGill Pain Questionnaire, which consists of both sensory and affective pain descriptors. Brain imaging tests were then conducted within one week of this clinical pain assessment. As hormonal status is known to influence pain processing, all premenopausal women underwent brain imaging between days 5-14 of their menstrual cycles. During the fMRI test, pressure stimulation was applied to the thumb and vulva (separately) at pressures consistent with the participant's previous rating of non-painful touch, faint pain, mild pain and slightly intense pain. Women's neural activity, associated with blood oxygen level dependent (BOLD) signals in response to pressure pain stimuli, were captured using a 3 tesla General Electric scanner at the University of Michigan fMRI lab. These activation maps were then statistically compared among the VVD, FM and healthy control groups using two-sample t-tests and ANOVA analyses.

As expected, we found that it took significantly less pressure to elicit vulvar and thumb pain in women with VVD compared to controls. Similarly, women with FM endorsed significantly lower pressure pain thresholds at the thumb. When analyzing the fMRI data collected during pressure pain testing of the thumb, both the FM and VVD groups had greater activation in the insula than did controls. In addition to the anterior and mid-insula, VVD patients also showed increased brain activity in several pain regions identified in other studies of patients with various pain disorders, including the dorsal mid-cingulate, posterior cingulate, bilateral secondary somatosensory cortex and ventral posterolateral nuclei of the thalamus. When analyzing activity in the entire brain in response to vulvar pressure testing, women with VVD did not display significantly altered brain activity compared to controls in any one region. However, when separately analyzing specific areas of the "pain matrix," VVD patients showed significantly less deactivation than did controls in the inferior parietal lobe, which is a task-negative structure, i.e., a brain region that is deactivated, rather than activated, during painful stimuli.

Further, we found significant differences in fMRI responses between some, but not all, of the previously proposed VVD subgroups. During thumb pressure testing, the 14 women with the primary form of the disorder showed greater brain activation at the posterior cingulate region compared to the eight with the secondary subtype. Significantly greater brain activity was also noted in the posterior cingulate region in the 14 women who had provoked-only pain versus the 10 who also had spontaneous pain. Interestingly, we found no differences in brain activity between women with generalized versus localized vulvar pain. During vulvar pressure testing, women with provoked pain had greater activation in the precuneus region versus those with unprovoked pain, but no other

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Brain Activity

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differences were found in our analysis of primary versus secondary VVD or generalized versus localized vulvar pain when testing at this location.

Our findings of augmented brain activity in response to a stimulus distant to the vulva, i.e., the thumb, implicates an underlying pathology involving the CNS, i.e., brain and spinal cord, in some women with vulvodynia. Interestingly, the augmented brain response seen in the pain-related brain areas (particularly the insula) in VVD patients was also found in women with fibromyalgia, suggesting that these two chronic pain states may share common underlying neurobiological pathology. Further, differing central activity between VVD subgroups suggests that there may be several different underlying pathologies. One can liken this to headache disorders and the different underlying mechanisms involved in migraine, tension type and cluster headaches.

These findings may impact clinical care as patients with more central brain pathology may respond differently to interventions that target the CNS (e.g., oral "pain-blocking medications") versus those that preferentially target the peripheral vulvar tissue, such as creams applied to the vulvar skin. These findings also suggest that measures of systemic sensitivity and presence of coexisting pain conditions, such as fibromyalgia, chronic headache and interstitial cystitis, may be important variables for inclusion in clinical trials investigating the effectiveness of VVD treatments. Based on the findings of this study, future research on clinical measures of CNS sensitivity, VVD subgroup identification using CNS responses and on the use of these measures in clinical trials assessing the effectiveness of vulvodynia treatments are both needed and warranted.

[Editor's Note: *The results of this study are reported in full in: Hampson JP, Reed BD, Clauw DJ, Bhavsar R, Gracely RH, Haefner HK, Harris RE.* J Pain. *2013 Jun; 14(6):579-89.]*

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